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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,366	09/26/2005	Masayuki Machida	040894-7170	1408

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,366	MACHIDA ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of October 10, 2007, to the Restriction Requirement dated September 10, 2007 has been entered. Claim 6 has been amended. No claims were cancelled or newly added. Claims 1-12 are pending in the application.

Election/Restrictions

Applicants' election of Group I (claims 1-5 and 9-12), drawn to a DNA fragment comprising a termination codon upstream of a lethal gene, and a recombinant vector comprising said DNA fragment is acknowledged. Applicants' election of colicin E3, as the species of lethal gene is further acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As the restriction is still deemed proper, the requirement for restriction is maintained and hereby made FINAL. It should be noted that in view of the search of the prior art, and upon further consideration, the restriction between Groups I and II is hereby withdrawn. Accordingly, claims 6-8 are re-joined to Group I claims. Applicants timely responded to the restriction (election) requirement in the reply filed September 14, 2007.

Claims 1-12 are under current examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 7-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Vernet et al. (Gene 34:87-93; 1985; of record), as evidenced by GenBank Accession No: V00083, 17 May 1995).

The claims embrace a DNA fragment in which one or at least two translation termination codons are inserted into the 5' upstream side of a colicin E3 lethal marker gene, and wherein a neutralizing gene for the lethal gene is conjugated to the 3' downstream side of the colicin E3 gene. The instant specification states that the neutralizing gene corresponds to the immunity E3 inhibitor for the colicin gene (p. 4, lines 23-24).

When given their broadest reasonable interpretation, the translation termination codons may be any termination codon inserted in any reading frame relative to the ColE3 lethal gene.

Claims 5 and 8 are directed to DNA fragments comprising nucleotide sequences represented by SEQ ID NOs: 18 or 19, and 15 respectively. The word "represent" may be defined as "to serve as the counterpart or image of" or "to take the place of in some respect" (Merriam-Webster Online Dictionary). Accordingly, SEQ ID NOS: 18 and 19 are represented by the colicin E3 gene; SEQ ID NO: 15 is represented by colicin E3 immunity gene.

Vernet et al. describe direct-selection vectors comprising ColE3 lethal gene as a positive selection marker, based on the inactivation of the lethal gene colicin E3 by the insertion of a foreign DNA fragment (Title and Abstract; limitation of claims 1, 4, 9, 10 and 11). Further describing the vector comprising the marker can be maintained within the *Escherichia coli* cells (Abstract; limitation of claim 10). The authors additionally describe vectors comprising the ColE3 lethal gene with the immunity gene present downstream thereof, and wherein restriction cleavage sites (EcoRV and KpnI respectively) are present in both terminal sides (p. 88, Fig. 1, pVT21; limitation of claims 2, 7 and 8). Fig. 1 additionally depicts the construction of plasmid vector pVT21 by insertion of the 1.85 kb Ap^R and ori region from pBR327, to the 5' upstream side of the colicin E3 gene, that necessarily contains at least one or two translation termination codons (limitation of claims 1 and 3). The sequence of the 1.85 kb region from pBR327 was well known in the prior art, as evidenced by GenBank Accession No: V00083.

Therefore by teaching all the limitations of claims 1-5 and 7-11, Vernet et al. anticipate the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 6-12 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vernet et al. (Gene 34:87-93; 1985; of record), in view of Hofte et al. (Eur. J. Biochem. 161:273-280; 1986).

The claims embrace a DNA fragment in which three translation termination codons are inserted immediately upstream side of a colicin E3 lethal marker gene, and wherein a neutralizing gene for the lethal gene is conjugated to the 3' downstream side of the colicin E3 gene. Claim 12, directed to a recombinant vector, which is free of an expression promoter for the colicin E3 lethal gene marker has been interpreted as directed to a vector that is devoid of the colicin E3 native promoter, because when given its broadest reasonable interpretation in view of the as-filed specification, for the colicin E3 gene to serve as a marker in a vector, would require expression from some operably linked promoter.

Claims 6 and 8 are directed to DNA fragments comprising nucleotide sequences represented by SEQ ID NOs: 14 and 15 respectively. The word "represent" may be defined as "to serve as the counterpart or image of" or "to take the place of in some respect" (Merriam-Webster Online Dictionary). Accordingly, SEQ ID NO: 15 is represented by colicin E3 immunity gene; and SEQ ID NO: 14 is represented by the colicin E3 gene having a colicin E3 immunity gene downstream thereof, and three termination codons inserted in-frame into the 5' upstream side of the colicin E3 gene comprising an active site.

Vernet et al. describe direct-selection vectors comprising ColE3 lethal gene as a positive selection marker, based on the inactivation of the lethal gene colicin E3 by the insertion of a foreign DNA fragment (Title and Abstract; limitation of claims 1, 9 and 11). Further describing the vector comprising the marker can be maintained within the *Escherichia coli* cells (Abstract; limitation of claim 10). The authors additionally describe vectors comprising the ColE3 lethal gene with the immunity gene present downstream thereof (p. 88, Fig. 1, pVT21; limitation of claim 7).

While Vernet et al. do not describe the insertion of three translation termination codons in-frame into the 5' upstream side of the active site of their ColE3 lethal gene, the insertion of in-frame termination codons upstream of genes for the prevention of read-through translation was well known in the prior art.

Hofte et al. describe a plasmid-encoded crystal protein gene (bt2; cloned from *Bacillus thuringiensis berliner* 1715), expressed in *Escherichia coli,* that encodes a toxic protein (Abstract). Hofte et al. specifically describe the construction of plasmid pLBkm25, comprising the bt2 gene under the control of the lambda P_L promoter, and "a fragment carrying three stop codons in the three reading frames to prevent read-through translation from an open reading frame" (Fig. 1 and first column, p. 274). As read-through translation occurs in the 5' to the 3' direction, the described stop codons must necessarily be inserted in-frame and at the 5' end of a gene, to prevent read-through translation (limitation of claim 6). Moreover, because the bt2 gene described by Hofte et al. includes 5' end deletions up to the 37th codon, and is under the control of the lambda P_L promoter (i.e. a heterologous promoter), it is free from the expression promoter of the lethal gene (i.e. its native promoter; limitation of claim 12).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Vernet et al. and Hofte et al., to include three in-frame termination codons and a heterologous promoter in the direct-selection cloning vector of Vernet et al., with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to insert three in-frame termination codons into the 5' upstream side of the colicin E3 gene, and place the gene under the control of an autologous gene expression system,

because the combination of elements would allow for greater control over the RNA and protein expression levels of the colicin E3 lethal gene.

Conclusion

Claims 1-12 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, A.U. 1633